PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
95.81434/04		

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB2004/003387	04.08.2004	04.08.2003

International Patent Classification (IPC) or national classification and IPC

B01J13/00, B01J13/02

Applicant

CAMURUS AB

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of four sheets, as follows:
      - ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06.06.2005	03.11.2005

Name and mailing address of the international preliminary examining authority:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Authorized Officer

Willsher, C

Telephone No. +31 70 340-2649

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/003387

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-64	as originally filed
Claims, Numbers	
1-32	received on 04.07.2005 with letter of 30.06.2005
Drawings, Sheets	
1/13-13/13	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded".*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-32
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-32
Industrial applicability (IA)	Yes:	Claims	1-32
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

1. Following receipt of claims 1-32 with the letter dated 30.06.05, full examination is possible. The observations made in the said letter are noted; nevertheless, the IPEA considers US-A-5 531 925 (Document D1) to be very relevant.

2. D1 describes a method in which a local, dispersible phase is created in the presence of a solvent within a homogenous non-lamellar phase, followed by fragmentation to form particles having an interior made of the homogeneous phase and a surface made of the dispersible phase; the local dispersible phase can be selected as lamellar (claim 7). D1 thus involves a dispersion of lamellar and optionally non-lamellar particles (which are also ampniphilic - see column 1, lines 10-11). Fragmentation can involve co-equilibriation with an amphililic substance at elevated temperature followed by rapid cooling, and can control particle size distribution (column 10, lines 30-31; column 10, line 66 to column 11, line 9; column 11, lines 24-26), and the solvent is most often water or any other polar solvent (column 8, lines 54-56; claims 13 and 33). Since in claim 7 of D1 a lamellar phase must be selected as the local dispersible phase, the method recited in present claim 1 is formally novel. However, its selection from claim 7 of D1 does not involve an inventive step, since D1 clearly indicates that particle size distribution can be controlled, which is also the technical problem posed in the present application (description, page 1, first paragraph).

3. Claims which depend on present claim 1 involve either results to be achieved - ie. no further technical details of the method are given - see claims 2-4 - or subject-matter which has not been shown as inventively contributing to solving the technical problem. The subject-matter of claims 2-14 thus does not involve and inventive step.

4. From the argumentation set forth in paragraph 2, above, the IPEA can see no inventive merit in the particles recited in present claims 15 and 16, and from the argumentation in paragraph 3, above, no inventive step for the subject-matter of present claims 17-32. In this respect, attention is drawn to the abstract of D1, as well as to column 27, lines 42-55).

5. Claims 1-32 are not allowable under Article 33(3) PCT.

81434/04.627

Claims

1. A method for forming a dipersion comprising non-lamellar amphiphile particles having improved phase behaviour, particle size distribution and/or storage stability, said method comprising forming a dispersion of lamellar and optionally non-lamellar particles comprising at least one structuring agent in a polar solvent, heating said particles to an elevated temperature, followed by cooling, wherein said heating is to a temperature and for a period sufficient to provide, after cooling, a measurable improvement in phase behaviour, particle size distribution and/or storage stability.

2. A method as claimed in claim 1 wherein said heating is to a temperature and for a period sufficient to provide conversion of at least 50% of said lamellar particles to non-lamellar form, after cooling.

3. A method as claimed in claim 1 wherein said heating is to a temperature and for a period sufficient to provide a narrowing of said particle size distribution, after cooling.

4. A method as claimed in claim 1 wherein said heating is to a temperature and for a period sufficient to provide stabilisation of said particle size distribution after cooling.

5. A method as claimed in any of claims 1 to 4 wherein said polar solvent is an aqueous solution.

6. A method as claimed in any of claims 1 to 5 wherein said particles are colloidal.

7. A method as claimed in any of claims 1 to 6 wherein said particles comprise at least 50% of a structure forming amphiphilic component "a", up to 40% of at least

one structure swelling agent "b" and up to 20% of a dispersion stabilising polymeric agent "c", wherein all parts are by weight relative to the total weight of a+b+c.

8. A method as claimed in any of claims 1 to 7 wherein said heating is to a temperature of 75 to 200 C.

9. A method as claimed in any of claims 1 to 8 wherein said heating is to an elevated temperature at which the equilibrium form of the particles is not non-lamellar.

10. A method as claimed in any of claims 1 to 8 wherein said heating is to an elevated temperature at which the equilibrium form of the particles is not liquid crystalline.

11. A method as claimed in claim 9 or claim 10 wherein said heating is to an elevated temperature at which the equilibrium form of the particles is L_2 phase.

12. A method as claimed in any of claims 1 to 11 wherein said heating is for a period of between 1 minute and 4 hours.

13. A method as claimed in any of claims 1 to 12 wherein said dispersion of lamellar and/or non-lamellar particles is formed by sonication and/or extrusion.

14. A method as claimed in any of claims 1 to 13 further comprising drying said particles.

15. Amphiphile particles comprising at least one structuring agent, wherein at least 75% of the particles are non-lamellar.

16. Amphiphile particles as claimed in claim 15 formed by the method of any of claims 1 to 14.

17. Amphiphile particles as claimed in claim 15 or claim 16 wherein the size distribution of said particles is essentially stable to storage in dispersion in a polar solvent at room temperature for at least 10 days.

18. Amphiphile particles as claimed in claim 15 or claim 16 wherein the size distribution of said particles is essentially stable to storage in dispersion at a concentration of 2% total amphiphile in a polar solvent at room temperature for at least 10 days

19. Amphiphile particles as claimed in any of claims 15 to 18 further comprising at least one active agent.

20. Amphiphile particles as claimed in claim 19 wherein said active agent is selected from human and veterinary drugs and vaccines, diagnostic agents, plant essential oils, plant extracts, aromas, cosmetic agents, nutrients, and dietary supplements.

21. Amphiphile particles as claimed in any of claims 15 to 20 wherein said particles are colloidal.

22. Amphiphile particles as claimed in any of claims 15 to 21 wherein said structuring agent is at least one selected from the group of natural lipids, synthetic lipids, surfactants and copolymers.

23. Amphiphile particles as claimed in claim 22 wherein said structuring agent is at least one selected from the group of glycerol monooleate (GMO), glycerol monolinoleate, diglycerol monooleate (DGMO), diglycerol monolinoleate, glyceryl dioleate, dioleyl phosphatidyl ethanolamine (DOPE), dioleyl phosphatidylcholine (DOPC), phytantriol, and mixtures thereof.

24. Amphiphile particles as claimed in any of claims 15 to 23 wherein said particles additionally comprise at least one fatty acid or fatty acid salt.

25. Amphiphile particles as claimed in any of claims 15 to 24 further comprising a fragmentation agent.

26. Amphiphile particles as claimed in claim 25 wherein said fragmentation agent is a polyethylene oxide copolymer, a lipid derivatised with polyethylene oxide, a hydrophobically modified polysaccaride, an amphiphilic protein or a mixture thereof.

27. Amphiphile particles as claimed in any of claims 15 to 26 comprising a structuring agent selected from glycerol monooleate (GMO), diglycerol monooleate (DGMO), glycerol dioleate, dioleyl phosphatidyl ethanolamine (DOPE) and mixtures of and further comprising a fragmentation agent selected from poloxamer 407, poloxamer 188, TMGO-15, dioleyl phosphatidyl ethanolamine-polyethyleneglycol (5000), polysorbate 80 and mixtures thereof.

28. Amphiphile particles as claimed in any of claims 15 to 26 wherein said particles comprise at least 50% of a structure forming amphiphilic component "a", up to 40% of at least one structure swelling agent "b" and up to 20% of a dispersion stabilising polymeric agent "c", wherein all parts are by weight relative to the total weight of a+b+c.

29. Amphiphile particles as claimed in any of claims 15 to 28 wherein the equilibrium form of the particles at room temperature is non-lamellar.

30. A dry powder comprising amphiphile particles as claimed in any of claims 15 to 29.

31. A gel or cream comprising amphiphile particles as claimed in any of claims 15 to 29.

32. A pharmaceutical composition comprising amphiphile particles as claimed in any of claims 15 to 29.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

SECOND AND SUPPLEMENTARY NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION (TO DESIGNATED OFFICES WHICH APPLY THE 30 MONTH TIME LIMIT UNDER ARTICLE 22(1))

(PCT Rule 47.1(c))

To:

FRANK B. DEHN & Co.
179 Queen Victoria Street
London EC4V 4EL
ROYAUME-UNI

File 81434/04
14 DEC 2005
Frank B. Dehn & Co.
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Date of mailing (day/month/year)	
08 December 2005 (08.12.2005)	
Applicant's or agent's file reference	IMPORTANT NOTICE
95 81434/004	

International application No	International filing date (day/month/year)	Priority date (day/month/year)
PCT/GB2004/003387	04 August 2004 (04.08.2004)	04 August 2003 (04.08.2003)

Applicant

CAMURUS AB et al

1. **ATTENTION** For any designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002 (30 months from the priority date), does not apply, please see Form PCT/IB/308(First Notice) issued previously.

2. Notice is hereby given that the following designated Office(s), for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, has/have requested that the communication of the international application, as provided for in Article 20, be effected under Rule 93*bis*.1. The International Bureau has effected that communication on the date indicated below.
17 February 2005 (17.02.2005)

AU, AZ, BY, CN, CO, DZ, EP, HU, KG, KP, KR, MD, MK, MZ, NA, RU, SY, TM, US

In accordance with Rule 47.1(c-*bis*)(i), those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

3. The following designated Offices, for which the time limit under Article 22(1), as in force from 1 April 2002, does apply, have not requested, as at the time of mailing of the present notice, that the communication of the international application be effected under Rule 93*bis*.1:

AE, AG, AL, AM, AP, AT, BA, BB, BG, BR, BW, BZ, CA, CR, CU, CZ, DE, DK, DM, EA, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, ID, IL, IN, IS, JP, KE, KZ, LC, LK, LR, LS, LT, LV, MA, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, SC, SD, SG, SK, SL, TJ, TN, TR, TT, UA, UZ, VC, VN, YU, ZA, ZW

In accordance with Rule 47.1(c-*bis*)(ii), those Offices accept the present notice as conclusive evidence that the Contracting State for which that Office acts as a designated Office does not require the furnishing, under Article 22, by the applicant of a copy of the international application.

4. **TIME LIMITS for entry into the national phase**

For the designated or elected Office(s) listed above, the applicable time limit for entering the national phase will, subject to what is said in the following paragraph, be **30 MONTHS** from the priority date.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain of the designated or elected Office(s) listed above. For regular updates on the applicable time limits (30 or 31 months, or other time limit), Office by Office, refer to the *PCT Gazette*, the *PCT Newsletter* and the *PCT Applicant's Guide*, Volume II, National Chapters, all available from WIPO's Internet site, at http://www.wipo.int/pct/en/index.html.

It is the applicant's **sole responsibility** to monitor all these time limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Nora Lindner
Facsimile No. +41 22 740 14 35	Facsimile No. +41 22 338 89 65

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